

Selenium: does selenium status have health outcomes beyond overt deficiency?

Possible protection against cancer and improved immune function make supplementation with selenium attractive, but its toxicity and other unknown effects urge caution

SELENIUM PRESENTS A NUTRITIONAL CONUNDRUM because of its dual status as a highly toxic, but essential, trace element.¹ The eightfold gap between the estimated average requirement² and the upper limit of safe intake is relatively narrow, so questions of too much and too little are important. Additional key questions pertain to adequate versus optimal status, and reflect the shift in focus of nutrition from preventing deficiency towards promoting optimal health. As is the case for many micronutrients, the quest for protective effects of selenium (Se) intakes above requirements is rapidly gaining momentum.

Ever since the biological role of Se in humans was first delineated less than 30 years ago, evidence for its increasing scope and importance to human health has been rapidly accumulating. Increasingly, Se depletion, as opposed to “deficiency”, is being associated with a range of health outcomes, including viral infection, reproduction, mood, thyroid function, cardiovascular disease, inflammatory conditions, immune function and cancer protection.^{3,4} It is possible to advance a range of theoretical arguments that suboptimal Se status may have an effect on health, but evidence of a direct relationship to health outcomes is very limited. Se research is incipient and there is a paucity of data. For example, Se reference values that have been adopted in the United States² are based on only two studies, one of which was a 1983 Chinese study of poor quality. Research is hampered by substantial difficulties in assessing and interpreting Se intakes and status, which become even more significant in the context of extreme global variations in the Se content of soil, food and human tissue.^{3,4}

We do know that Se has key roles in redox regulation and antioxidant function, and hence in membrane integrity, energy metabolism and protection against DNA damage.^{1,3,4} These and other functions are mediated through over 35 selenoproteins, which require adequate Se intake for synthesis and expression. Selenoproteins include several forms of the enzymes glutathione peroxidase (GPx), thio-reductase and iodothyronine 5'-deiodinase. The number of known selenoproteins has almost trebled over

the past 7 years,^{1,3} although the roles of several remain undefined.

Plasma Se concentration is the most commonly used indicator of Se status.² Low Se intakes, plasma Se concentrations and GPx activities have direct, linear associations up to a threshold plasma Se concentration (70–100 µg/L), beyond which GPx activity plateaus. This maximum GPx concentration is thought to represent repletion, and commensurate Se intake forms the basis of recommended dietary requirements.^{2,5} Concentrations of other selenoproteins are also influenced by Se intake and may have a role as functional indicators of Se status,^{2,3,5} but assay methods and reference standards are at an early stage, and comparisons between studies are difficult. There is differential hierarchical expression of the selenoproteins, with relative preservation of the presumably more metabolically important at lower intakes of Se.^{1,3} However, we do not clearly understand the health implications of submaximal expression of the selenoproteins.

There are enormous geographical variations in the Se content of soil and food, and hence in Se intakes and concentrations in human blood and tissues.^{3,4,6} Thus, it is essential to use local data for monitoring and interpreting Se status.⁶ The 2000 US Recommended Dietary Allowance (RDA) is 55 µg/day.² The 1987 Australian RDAs are 70 µg/day for women and 85 µg/day for men, but these are currently under review.⁷ Organic selenomethionine is the predominant form of Se in food. The most important dietary sources of Se are meat, poultry, fish and cereals (although brazil nuts are very high in Se and certain fish also have particularly high levels). Accurate assessment of intake is exceptionally difficult because the Se content of food is so variable.^{2,3,6,8} Estimates of Se intakes include 106 µg/day in a large representative US sample,² and a range of 29–70 µg/day in Europe.³ Extremely limited Australian data suggest intakes of around 90 µg/day,⁶ while more comprehensive New Zealand data show intakes as low as 28 µg/day, and indicate that conventional dietary intake methods are inadequate for estimating Se intake.⁸ Inorganic Se (selenite and

selenate) is only available through supplementation, is generally less bioavailable and produces a different physiological response than organic forms of Se.^{1,2}

Environmental changes and agricultural practices may be reducing Se concentrations in soil.⁴ These factors, in conjunction with trade barriers (eg, the cessation of importing high-Se US wheat to the European Union), appear to be associated with a decline in the availability of Se through the food chain and in human Se status, particularly in Europe.³ Changes in food supply and habits, including the importation of Australian wheat, have improved the previously marginal Se status of New Zealanders.⁹ Twenty-six European studies since 1990 all reported mean plasma Se concentrations below 100 µg/L, the level postulated to be required for GPx saturation and cancer protection.^{3,10} Ten of these studies reported plasma Se levels under 70 µg/L,³ postulated by others to be associated with GPx saturation.¹¹ A representative US plasma Se level was 124 µg/L.² In this issue of the Journal (*page 383*), Lyons and colleagues present evidence that although mean plasma Se concentrations of South Australians are relatively high by European standards, they may be declining, and over a third of their sample had levels below 100 µg/L.¹²

Overt human Se deficiency is rare. It is manifested as Keshan disease, an endemic fatal cardiomyopathy, which is virtually unknown outside areas of China, where the levels of Se in soil and dietary Se intake are extremely low. A few studies have reported Se deficiency as a result of long-term total parenteral nutrition.¹ Despite myriad claims for potential relationships between a range of diseases and Se status, there are no clear population health outcomes that can be attributed to Se status in countries like New Zealand, where intakes are very low.^{1,9}

The evidence for an effect of Se on health outcomes is strongest in cancer prevention. Secondary findings from the 10-year US Nutritional Prevention of Cancer Trial demonstrated a protective effect of supplementation with 200 µg/day of organic Se (from yeast) on total cancer incidence and mortality, and on prostate cancer incidence (relative risk, 0.75, 0.59, and 0.48, respectively).¹⁰ The effects were stronger in men and in those with lower baseline plasma Se levels (< 105 µg/L), and were not found for a range of other site-specific cancers. Of concern is that in the top tertile for baseline plasma Se level there may be an association between supplementation and increased risk of breast cancer and melanoma, as well as overall cancer incidence.¹⁰ There are numerous limitations to what was a small study, and the relatively high baseline plasma Se levels (114 µg/L) make it difficult to generalise the findings. It appears that protection from cancer may require supplementation beyond correction of depletion and maximal expression of the selenoproteins. Several large trials are under way to clarify the benefits and risks of Se supplementation with respect to tumorigenesis.

More speculative and tantalising is the potential association between Se and immune function. Evidence suggests that reduced Se status may be associated with the incidence of clinical infection in adults,¹³ and supplementation of

apparently Se-replete individuals potentially enhances immune function.³ Animal studies indicate that the Se status of the host can genetically alter invading viral pathogens, so that a normally benign strain may become virulent in an Se-deficient host.¹⁴ This is of interest given the emergence of new influenza virus strains from China, where there are significant areas of overt Se deficiency, and given the decline in Se status associated with progression of HIV infection.³

In summary, there has been an explosion of interest in the biological role of Se and the potential health implications of Se status. Much of the evidence in humans is descriptive, and the dearth of quality prospective trials means the links with many diseases are still controversial and, in many cases, speculative. There are very limited representative data on Se content of the food supply and Se status in many populous parts of the world, and no nationally representative Australian data. Lyons and colleagues provide the most comprehensive Australian plasma Se data to date,¹² but they are neither prospective nor representative, and there may be variations according to states.⁶ Outcomes of research on Se in the next decade are likely to be important, and we urgently need more Australian data.

Meanwhile, it is necessary to remember that selenium is toxic.¹⁻³ Intakes below 400 µg/day are considered safe for almost all individuals.² As illustrated by the Nutritional Prevention of Cancer Trial,¹⁰ outcomes of Se supplementation are variable and may not be without risk. Benefits and an appropriate dose for supplementation remain controversial. Until further evidence is available, supplementation should be recommended with caution, and overconsumption should be avoided.³

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